PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

ARAVA 10 mg film-coated tablets

ARAVA 20 mg film-coated tablets

Leflunomide

Contains sugar (lactose monohydrate)

Read all of this leaflet carefully before you start taking ARAVA

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- ARAVA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What ARAVA is and what it is used for

ARAVA contains the active substance leflunomide, which belongs to a group of antirheumatic medicines called “disease-modifying antirheumatic medicines”.

ARAVA is used to treat active rheumatoid arthritis in adults.

It works by slowing down the process of joint damage and relieves the symptoms of the disease, such as inflammation of joints, swelling, difficulty moving and pain.

2. What you need to know before you take ARAVA

Do not take ARAVA if

- You have ever had an allergic reaction to leflunomide (especially a serious skin reaction, often accompanied by fever, joint pain, red skin stains, or blisters, e.g. Stevens-Johnson syndrome) or to any of the other ingredients of ARAVA listed in section 6, or if you are allergic to teriflunomide (used to treat multiple sclerosis). Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of your lips, face, throat or tongue (see section 4. Possible side effects).
- You have any liver problems.
- You suffer from any problem which affects your immune system (e.g. AIDS).
- You have any problem with your bone marrow, or if you have low numbers of red or white cells in your blood or a reduced number of blood platelets.
- You are suffering from a serious infection.
- You have moderate to severe kidney problems.
- You have severely low numbers of proteins in your blood (hypoproteinaemia).
- You are pregnant, think you may be pregnant, or you are a woman of childbearing potential and are not using reliable contraception (Pregnancy must be excluded with a pregnancy test before the start of treatment).
- You are breastfeeding.
- You are male: reliable contraception must also be guaranteed as there is a possibility of male mediated harm to the unborn baby by men using ARAVA.
- You are younger than 18 years of age.

Do not take ARAVA if any of the above applies to you. If you are not sure, talk to your doctor before taking ARAVA.

Warnings and Precautions

Tell your doctor or health care provider before taking ARAVA if:

- You have ever suffered from inflammation of the lung (interstitial lung disease).
- You have ever had tuberculosis (a bacterial infection that usually attacks the lungs, but also other parts of the body) or if you have been in close contact with someone who has or has had

tuberculosis. Your doctor may perform tests to see if you have tuberculosis and monitor you during treatment if necessary.

Take special care with ARAVA:

- Before you start taking ARAVA and at regular intervals during treatment with ARAVA, your doctor will carry out blood tests to monitor your blood cells and liver. Your doctor will also check your blood pressure regularly as ARAVA can cause an increase in blood pressure.
- In certain circumstances (e.g. you develop serious side effects, you need to change to a different antirheumatic treatment or in case of a desired pregnancy) your doctor will decide to stop your treatment with ARAVA. However, ARAVA does not clear quickly from your body and therefore your doctor may speed up excretion of ARAVA from your body with medicines such as colestyramine or activated charcoal.
- ARAVA can occasionally cause some problems with your blood, liver, lungs, or nerves in your arms or legs. It may also cause some serious allergic reactions (including drug reaction with eosinophilia and systemic symptoms (DRESS)), or increase the chance of a severe infection. For more information on these, please see section 4.

  DRESS appears initially as flu-like symptoms and a rash on the face, then an extended rash with a high temperature, increased levels of liver enzymes seen in blood tests and an increase in a type of white blood cell (eosinophilia) and enlarged lymph nodes.
- Tell your doctor without any delay if you develop symptoms such as unusual tiredness, abdominal pain, or jaundice (yellow discolouration of the eyes or skin). Such symptoms may indicate the development of liver disorders, which may need special action by your doctor.
- Infections might become more severe than usual while taking ARAVA, because ARAVA may reduce your body's ability to fight back infections. Therefore, symptoms suggestive of an infection (e.g. fever, sore throat and cough) must be reported to your doctor immediately to ensure early and vigorous treatment.
- Tell your doctor without any delay if you have symptoms such as paleness, tiredness, and increased proneness to infection or bruising. Such symptoms may point to the existence of blood cell disorders, which may need discontinuation of ARAVA and other medications, and further action by your doctor.

- Tell your doctor if you have unexplained chronic diarrhoea. Your doctor may perform additional tests for differential diagnosis.
- ***Male patients:*** As it cannot be excluded that ARAVA passes into semen and increases the risk of malformation in newborn infants, reliable contraception should be used during treatment with ARAVA. If you wish to father a child, you should contact your doctor. Your doctor will advise you to stop taking ARAVA and take certain medicines to remove ARAVA rapidly and sufficiently from your body. You will then need a blood test to make sure that ARAVA has been sufficiently removed from your body first.

If you are not sure if any of the above applies to you, talk to your doctor or healthcare professional.

Other medicines and ARAVA

Always tell your doctor or health care provider if you are taking any other medicines (including complimentary or traditional medicine). This is because ARAVA can affect the way some other medicines work. Also, some medicines can affect the way ARAVA works.

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you are taking:

- teriflunomide, used for multiple sclerosis (combined use with ARAVA is not recommended)
- other medicines for rheumatoid arthritis such as antimalarials (e.g. chloroquine and hydroxychloroquine), intramuscular or oral gold, D-penicillamine, azathioprine and other immunosuppressive medicines (e.g. methotrexate) as these combinations are not advisable, since it may lead to increased risk for blood or liver side effects
- warfarin and other oral medicines used to thin the blood; close monitoring of your INR is necessary
- repaglinide or pioglitazone, for diabetes
- daunorubicin, doxorubicin, paclitaxel, or topotecan for cancer
- rifampicin, for tuberculosis
- duloxetine for depression, urinary incontinence or in kidney disease in diabetics
- theophylline for asthma
- oral contraceptives (containing ethinylestradiol and levonorgestrel)
- cefaclor, benzylpenicillin (penicillin G), or ciprofloxacin for infections

- cimetidine (used to treat certain types of stomach ulcers and certain conditions with too much acid)
- indometacin, ketoprofen for pain or inflammation
- furosemide for heart disease (diuretic, water pill)
- zidovudine for HIV infection
- rosuvastatin, simvastatin, atorvastatin, pravastatin for hypercholesterolaemia (high cholesterol)
- sulfasalazine for inflammatory bowel disease or rheumatoid arthritis
- a medicine called colestyramine (used to reduce high cholesterol) or activated charcoal as these medicines can reduce the amount of ARAVA which is absorbed by the body.

If you are already taking a nonsteroidal anti-inflammatory medicine (NSAID) and/or corticosteroids, you may continue to take them after starting ARAVA.

Vaccinations:

If you have to be vaccinated, ask your doctor for advice. Certain vaccinations should not be given while taking ARAVA, and for a certain amount of time after stopping treatment.

ARAVA with food, drink and alcohol

ARAVA may be taken with or without food.

It is not recommended to drink alcohol during treatment with ARAVA. Drinking alcohol while taking ARAVA may increase the chance of liver damage.

Pregnancy and breastfeeding

Pregnancy:

Do not take ARAVA if you are or think you may be pregnant. If you are pregnant or become pregnant while taking ARAVA, the risk of having a baby with serious birth defects is increased. Women of childbearing potential must not take ARAVA without using reliable contraceptive measures.

Tell your doctor if you plan to become pregnant after stopping treatment with ARAVA, as you need to ensure that all traces of ARAVA have left your body before trying to become pregnant. This may

take up to 2 years. This may be reduced to a few weeks by taking certain medicines which speed up removal of ARAVA from your body (a “washout” procedure).

In either case it should be confirmed by a blood test that ARAVA has been sufficiently removed from your body and you should then wait for at least another month before you become pregnant. Your doctor will advise you on the washout procedure as well as the laboratory tests required.

If you suspect that you are pregnant while taking ARAVA or in the two years after you have stopped treatment, you must contact your doctor immediately for a pregnancy test. If the test confirms that you are pregnant, your doctor may suggest treatment with certain medicines to remove ARAVA rapidly and sufficiently from your body, as this may decrease the risk to your baby.

Breastfeeding:

Do not take ARAVA when you are breastfeeding, as leflunomide passes into the breast milk.

Driving and using machines

ARAVA may cause side effects such as dizziness that could affect your ability to drive while taking ARAVA. If this happens, do not drive or use any tools or machines.

ARAVA contains sugar

ARAVA tablets contain lactose monohydrate which may have an effect on the control of your blood sugar if you have diabetes mellitus (see section 6 - What ARAVA contains).

Patients with the rare hereditary conditions of lactose or galactose intolerance should not take ARAVA.

3. How to take ARAVA

Do not share medicines prescribed for you with any other person.

Always take ARAVA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

Your doctor will tell you how many ARAVA tablets to take, at what time and for how long.

The usual starting dose is ARAVA 100 mg daily (5 x 20 mg tablets daily) for the first three days. After this, most patients need a dose of ARAVA 10 mg or 20 mg once daily, depending on the severity of the disease.

ARAVA may be taken during meals or at any time between meals. Swallow the tablet whole with sufficient liquid.

It may take about 4 to 6 weeks or longer until you start to feel an improvement in your condition.

You will normally take ARAVA over long periods of time.

If you take more ARAVA than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take ARAVA

If you forget to take your tablets, take them as soon as you remember on the same day. If it is nearly time for the next dose, take the next dose as usual. Do not take a double dose to make up for the forgotten tablets.

If you stop taking ARAVA

After stopping ARAVA, traces of ARAVA will remain in your body for up to 2 years. If ARAVA was stopped due to serious side effects or pregnancy, or planned pregnancy (both male and female patients), your doctor may reduce the levels of ARAVA in your body within a few weeks by giving you certain medicines which speed up the removal of ARAVA from your body. Speak to your doctor if this is applicable to you.

4. Possible side effects

ARAVA can have side effects.

Not all side effects reported for ARAVA are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking ARAVA, please consult your health care professional for advice.

If any of the following happens, stop taking ARAVA and tell your doctor immediately or go to the casualty department at your nearest hospital:

Less frequent:

- Serious allergic reactions. Signs may include: a rash, swelling of your lips, face, throat or tongue which may cause difficulty breathing, weakness, light-headedness or dizziness and collapse.
- If you develop a skin rash or ulcers in your mouth, as these may indicate severe, sometimes life-threatening reactions such as:
  - Stevens-Johnson syndrome (blistering of the skin, mouth, eyes and genital area, red/purple rash, fever, headache, cough and joint pain) or erythema multiforme (blotchy red skin rash)
  - toxic epidermal necrolysis (severe extensive skin damage, e.g. separation of the epidermis (surface layer of the skin) and superficial mucous membranes).

Frequency unknown:

- Drug reaction with eosinophilia and systemic symptoms (DRESS), a medicine hypersensitivity reaction which affects your internal organs and increases the white cells (eosinophilia) in your blood. See: Warnings and precautions above.

These are all very serious side effects. If you have them, you may have had a serious allergic or other reaction to ARAVA. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

Frequent:

- The following symptoms of blood disorders which your doctor may determine with blood tests: getting infections more easily than normal, fever, sore throat, mouth ulcers or tiredness. This may be due to a low or abnormal number of white blood cells in your blood (leucopenia or agranulocytosis).

Less frequent:

- The following symptoms of blood disorders which your doctor may determine with blood tests:
  - bruising more easily than usual or you may have a rash of dark red spots under the skin (low number of blood platelets in your blood (thrombocytopenia))
  - chills, tiredness, unusually pale skin colour, shortness of breath, fast heartbeat or dark coloured urine (low number of certain blood cells, e.g. red blood cells (anaemia) or decrease in the number of all blood cells (pancytopenia))

- weight loss, night sweats and fever (eosinophilia).

- Severe infections and sepsis which may be life-threatening (infections may start with symptoms such as fever, sore throat or cough).
- Inflammation of the liver (hepatitis) which may be fatal. Symptoms may include tiredness, abdominal pain, yellow discolouration of the eyes or skin.
- Jaundice (yellow discolouration of the eyes or skin).
- Cough or breathing problems as these may indicate problems of the lung, (e.g. interstitial lung disease) which may be fatal.
- Unusual tingling, numbness, burning, weakness or pain in your hands or feet as these may indicate problems with your nerves (peripheral neuropathy).
- Problems with the nerves of the arms or legs (peripheral neuropathy).
- Severe increase in blood pressure.
- Inflammation of the pancreas, which causes severe pain in the abdomen and back (pancreatitis).

Frequency unknown:

- Kidney failure (symptoms may include decreased urine production and swelling of your arms and legs).
- Pulmonary hypertension (High blood pressure in the blood vessels that supply the lungs) Symptoms may include cough or breathing problems.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you have any of the following:

Frequent:

- mild allergic reactions (e.g. rashes, itching)
- headache, dizziness
- abnormal skin sensations like tingling (paraesthesia)
- mild increase in blood pressure
- diarrhoea
- colitis (inflammation of the inner lining of the colon, leading to diarrhoea and pain)
- nausea, vomiting

- inflammation of the mouth or mouth ulcers
- abdominal pain
- loss of appetite
- weight loss
- an increase in some liver laboratory test results
- eczema, dry skin, rashes, itching
- increased hair loss
- tenosynovitis (inflammation of the fluid-filled sheath that surrounds a tendon, usually in the feet or hands)
- tiredness (asthenia).

Less frequent:

- inflammation of your small blood vessels (may cause red sports on the skin, often the lower legs (vasculitis))
- a decrease in the levels of potassium in the blood
- anxiety
- taste disturbances
- urticaria (nettle rash)
- tendon rupture.

Frequency unknown:

- skin ulcer (A round, open sore in the skin through which the underlying tissues can be seen)
- an increase of certain enzymes in the blood (creatine kinase (CK))
- an increase in the levels of fat in the blood (cholesterol and triglycerides)
- a decrease in the levels of phosphate and uric acid in the blood
- cutaneous lupus erythematosus (characterized by rash on skin areas that are exposed to light)
- pustular psoriasis (psoriasis with fluid-filled bumps) or worsening psoriasis (scaly red skin patches)
- male infertility (which is reversible once treatment with this medicine is stopped).

If you notice any side effects not listed in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

You can report any side effects directly to Sanofi's Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

You can also report side effects to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of ARAVA.

5. How to store ARAVA

Store your tablets at or below 25 °C in the original container. Keep the bottle tightly closed.

Do not use your tablets after the expiry date shown on the container.

Store all medicines out of reach of children.

Return all left-over medicine to your pharmacist or clinic.

Do not dispose of unused medicine in the drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What ARAVA contains

- The active substance in ARAVA is leflunomide. Each ARAVA 10 mg tablet contains 10 mg leflunomide and each ARAVA 20 mg tablet contains 20 mg leflunomide.
- The other ingredients are colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, maize starch and povidone.
- Film coating: hypromellose, macrogol 8000, talc and titanium dioxide. The 20 mg tablet also contains yellow ferric oxide.
- Contains sugar (lactose): ARAVA 10 mg contains 78 mg lactose monohydrate per tablet and ARAVA 20 mg contains 72 mg lactose monohydrate per tablet.

What ARAVA looks like and contents of the pack

ARAVA 10 mg: White to almost white, round, film-coated tablets with a diameter of 7 mm.

Embossment: ZBN.

ARAVA 20 mg: Yellowish to ochre, spherical, triangular, film-coated tablets with a height of 7 mm.

Embossment: ZBO.

ARAVA 10 mg: 30 tablets in a plastic bottle.

ARAVA 20 mg: 30 tablets in a plastic bottle.

Holder of Certificate of Registration

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This leaflet was last revised in

28 January 2022

Registration numbers

ARAVA 10 mg: 33/3.1/0290

ARAVA 20 mg: 33/3.1/0291